DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 21 2004

Certified Mail
Return Receipt Requested

Gilbert Godin
President and CEO
MDS Pharma Services
The Triad
2200 Renaissance Blvd., Suite 400
King of Prussia, PA 19406-2755

Dear Mr. Godin:

Between September 13 and October 1, 2004, Susan F. Laska, Sriram Subramaniam, Ph.D., Martin K. Yau, Ph.D., Michael F. Skelly, Ph.D., Nilufer M. Tampal, Ph.D. and Jacqueline A. O'Shaughnessy, Ph.D., representing the Food and Drug Administration (FDA), inspected several bioequivalence studies conducted by MDS Pharma Services (MDS) in Saint-Laurent, Montréal (Québec) Canada, including the following:

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|---|---|---|---|
| Study [ | ][ ][ | ]Tablets | |
| Studies [ | ] and [ | ], [ ][ | ]Tablets |
| Studies [ | ] and [ | ].[ ][ | ]Tablets |
| Studies [ | ] and [ | ].[ ][ | ] Suspension |
| Studies [ | ] and [ | ][ ][ . | ] Tablets |

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research, to ensure that the rights, safety, and welfare of the human subjects of the study have been protected, and to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 320, Bioavailability and Bioequivalence Requirements.

This inspection was conducted subsequent to previous FDA inspections and correspondence to MDS documenting significant deficiencies at this facility. FDA initially inspected [ ] Study [ ] in July 2003 and concluded that you failed to conduct a thorough and systematic evaluation of the contamination that occurred during study sample analysis, resulting in the submission of invalid data to FDA. After the July 2003 FDA inspection, you made minor modifications to the original analytical method and reanalyzed the [ ] study samples in October/November 2003. FDA inspected the reanalyzed data in February 2004 and found that you made the minor modifications without conducting a systematic investigation to identify the source of contamination in the original method. On April 26, 2004, FDA sent you a letter discussing your inadequate approach to investigating sources of contamination in bioequivalence studies and your lack of policies and procedures to address such contamination issues. At your request, FDA met with representatives of MDS on August 10, 2004 to discuss outstanding issues

related to these inspections and FDA's letter to you.

At the conclusion of the current inspection, our personnel presented and discussed with [ ] [ ] C.A., the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including the letters from you and [ ] Ph.D. dated November 12, 2004 in response to Form FDA 483, we conclude that you failed to demonstrate that the analytical methods used in several in vivo bioavailability studies conducted in your facility could accurately measure the actual concentration of the active drug ingredient, or its active metabolite, achieved in the body, as required by 21 CFR 320.29(a). Specifically, we found a systemic problem of inadequate analysis and investigation of anomalous results across multiple studies for multiple sponsors. Because you failed to resolve numerous unexpected results, your analytical methods were not demonstrated to be accurate when utilized in the following bioequivalence studies:

[ ] [ ] Study [ ]

This study used the same analytical method ([ ]) as the invalid [ ] study for [ ] Our inspection confirmed evidence of contamination in the [ ] study similar to that found in the [ ] study. Specifically, blanks, calibration standards, quality control and subject samples exhibited unexpectedly high concentrations of [ ] and [ ] As was the case with the [ ] study, you selectively reanalyzed some study samples and found results significantly lower than the original values; in this case there were differences as great as 10-fold to 120-fold. As we explained in our April 26, 2004 letter, selective reanalysis of samples is not a scientifically valid method of addressing contamination; our letter also outlined the steps that should have been taken to address this contamination issue. Because you failed to resolve fully the contamination issue, investigate the cause of these unexpected results, and determine the total number of samples affected by contamination, the reported study data cannot be considered accurate and are not acceptable for review. We are aware that you recommended to the sponsor [ ] on September 8, 2004 that all the study samples should be reanalyzed, due to contamination in the original analysis. It is our understanding that the sponsor agreed on September 10, 2004.

[ ] [ ] Studies [ ] and [ ]
[ ] [ ] Studies [ ] and [ ]

The [ ] [ ] studies ([ ] and [ ]) and the [ ] [ ] studies ([ ] and [ ]) used a [ ] method similar to that used in the invalid [ ] study, except that the calibration range was narrower (i.e., [ ] instead of [ ] for [ ]. Our inspection of these studies found evidence of contamination similar to that found in the [ ]) and [ ] studies. For example, you selectively reanalyzed the study samples you flagged as anomalous and found significant differences between a majority of the original and repeat results; in these studies, the differences ranged from 2-fold to 358-fold. You failed to investigate the cause of these unexpected results, or the total number of samples affected by contamination. Thus, the reported concentration results cannot be considered accurate.

Following a review of your response to FDA Form 483 (letter dated November 12, 2004) we conclude that your response is deficient for the following reasons:

- In your response dated November 12, 2004, you identified truncation of the calibration range as one of three measures put in place to assure accurate data in your modified analytical method for [ ]. In your response dated September 8, 2004, you also identified the broad range of concentrations (e.g., the [ ] calibration range) in the analytical batches as a key reason for the variability in the invalid [ ] study. However, the [ ] and [ ] studies used the same upper calibration limit as the reanalyzed [ ] study ([ ] for [ ]) yet still yielded anomalous results. Therefore, your own data fail to demonstrate that a truncated calibration range corrects, or even relates to, the contamination issues in your analytical method for [ ].
- In your response dated November 12, 2004, you claimed that the risk of contamination was potentially increased in the [ ] and [ ] studies because the Cmax samples were not pre-diluted. You based this claim on the assertion that pre-dilution of Cmax samples would minimize the risk of contamination. You believed that pre-dilution was necessary in the reanalyzed [ ] study because some Cmax concentrations greatly exceeded the [ ] [ ] calibration limit for [ ] and were adjacent to study samples with low levels. However, the majority of the Cmax concentrations in the [ ] and [ ] studies (~90%) were within the calibration limit for [ ] and were similar to the diluted Cmax concentrations in the reanalyzed [ ] study. Therefore, there is no basis to conclude that pre-dilution would correct the contamination issues.

In summary, neither of these claims was shown to be scientifically valid and your own data contradict these claims.

Your letter dated September 8, 2004 also stated that MDS decided to review all [ ] bioequivalence studies. Our inspection revealed that you only evaluated studies pending FDA review (e.g., you did not review studies that supported applications that are now approved). In that letter, you also stated that you identified one [ ] study [ ] with problems similar to the [ ] study. As discussed above, our inspection found evidence of contamination in the [ ] and [ ] studies as well. The limited scope of your review of [ ] bioequivalence studies, and the apparent failure of that review to identify contamination in at least 4 additional studies, causes FDA to have concerns about the manner in which you investigated your operations and procedures to assure FDA that the analytical methods you used in other bioequivalence studies were accurate.

[ ] [ ] Studies [ ] and [ ]
[ ] [ ] Studies [ ] and [ ]

The analytical method for these studies used the [ ] to aliquot samples and an online extraction procedure. We note that sample processing for this analytical method was different from the [ ] studies above, and did not use the [ ]. Our inspection found that numerous study samples at various time points did not have measurable

concentrations of [ ] even though [ ] should have been present (e.g., time points near Cmax). Chromatograms for these samples showed an internal standard peak, but the [ ] peak was either absent or below the limit of quantitation (BLQ). Because measurable [ ] concentrations were found in the time points surrounding these samples, the BLQ results were unexpected. You failed to investigate the cause of these anomalous results, or reassay the affected samples. Because of these missing values, the reported pharmacokinetic parameters (Cmax and AUC) cannot be considered accurate. The data used to assess bioequivalence in these studies was not demonstrated to reliably reflect the actual concentration of [ ] achieved in the body at certain time points.

In summary, we wish to emphasize that our recent inspection identified multiple studies in addition to the [ ] study in which you failed to properly investigate anomalous results (4 [ ] and 4 [ ] studies). We believe that these findings may indicate a more widespread problem at your facility. As a result, FDA has concerns about the validity of other bioequivalence data generated by MDS, including data submitted in support of currently-approved applications. FDA recommends that you review the validity of bioequivalence studies you conducted within the last 5 years. We suggest that you meet with the FDA to discuss a plan to address our concerns. FDA is considering various options to verify the validity of submitted data. FDA's evaluation of such data could result in rejection of data where circumstances warrant and, for approved products, possible reconsideration of a product's therapeutic equivalence rating.

If you have questions or concerns about the issues raised in this letter, please reply to:

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Sincerely,

Joanne L Rhoads M.D.

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